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Review Article

Stent placement in benign esophageal strictures

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ABSTRACT

For benign esophageal strictures, the primary treatment is balloon dilation. However, approximately 10% of the strictures are not improved after balloon dilation and are defined as refractory benign esophageal strictures. The main causes of refractory benign esophageal strictures are esophageal surgery, caustic injury, and radiotherapy. Self-expandable stents, used primarily for the palliation of malignant esophageal strictures, are now used for refractory benign strictures due to the evolution of stent materials and designs. Fully covered, self-expandable metallic stents are the most commonly used. However, major complications such as tissue overgrowth and stent migration make the long-term results unfavorable. Recent studies of biodegradable stents and drug-eluting stents have shown encouraging results which may help to reduce the major complications.

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Keywords: Esophageal stenosis; Hyperplasia; Stent migration; Stents

Introduction

Balloon dilation is the treatment of choice in the management of benign esophageal strictures, although some patients require repeat dilations. The efficacy depends primarily on the etiology and complexity of the stricture. It has been reported that the recurrence rates of dysphagia after balloon dilation were 50% in anastomotic strictures, 72% in corrosive strictures, and 46% in radiation fibrosis.^{1–3} The corrosive stricture showed the poorest response after balloon dilations, especially at the early (from three weeks to six months after caustic injury) or late chronic stage.⁴ The strictures secondary to severe radiation fibrosis are also very tight and sometimes cannot even be dilated up to 10 mm in diameter. In addition to the etiology, the complexity of the stricture is also found to affect the dilation prognosis. The strictures have been divided into two categories according to their complexity, i.e., simple and complex. Simple strictures are focal (< 2 cm in length), straight, and wide enough to allow the passage of a normal-diameter endoscope. Complex strictures are long (> 2 cm in length), tortuous, and with a small diameter which precluded the passage of a normal-diameter endoscope.⁵ Regarding the causes of complex strictures, the most common are caustic ingestion, radiation injury, and surgery.^{6,7} Compared with simple strictures, complex strictures easily recur within weeks and are associated with a higher risk of complications. Approximately 10%

of benign esophageal strictures, which are mostly composed of complex strictures and show no improvement even after several dilation sessions (for example, the inability to achieve or maintain a diameter of 14 mm despite dilation every two to four weeks), are, therefore, named refractory strictures.^{8,9}

Several treatment methods have been used for refractory strictures, such as surgery, steroid injection, and stent placement. Although the surgeries of gastric pull-up and enteral replacement are potentially curative, the procedure-related morbidity and mortality rates are high. Therefore, many patients are unsuitable for surgery or unwilling to undergo surgery.^{10,11} Regarding endoscopic steroid injection, it showed limited efficacy in one randomized trial.¹² On the contrary, an increasing number of clinical studies support the use of stents for benign esophageal strictures due to their favorable results. Table 1 lists some commonly used fully covered metallic stents, plastic stents, and biodegradable stents.

Self-Expandable, Esophageal, Metallic Stents

The development of self-expandable metallic stents for benign strictures: from uncovered to covered

Before the invention of self-expandable metallic stents, rigid prosthesis such as the Celestin tube and Atkinson's tube were used for malignant esophageal strictures. However, the placement

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Table 1 Selected Overview of Fully Covered Metallic Stents, Plastic Stents, and Biodegradable Stents

Stent	Manufacturer	Material	Membrane	Shape	Diameter (body/flare, mm)	Length* (cm)	Braided	Specific feature
Niti-S	Taewong Medical (Gimpo, Korea)	Nitinol	Silicone	Dumbbell	16/20 18/23 20/25	8/10/12/14	Yes	
Evolution	Cook Medical (Bloomington, IN, USA)	Nitinol	Silicone	Dumbbell	18/23 20/25	8/10/12.5/15	Yes	Unretrievable
Wallstent	Boston Scientific (Natick, MA, USA)	Nitinol	Silicone	Dumbbell	18/23 23/28	10/12/15	Yes	
Alimaxx-E	Alveolus (Charlotte, NC, USA)	Nitinol	Polyurethane	Dual-flared	18/22	7/10/12	No	Antimigration struts
Polyflex	Boston Scientific	Polyester	Silicone	Solo-flared	16/20 18/23 21/28	9/12/15	Yes	Plastic
SX-ELLA	ELLA-CS (Hradec Kralove, Czech)	Polydioxanone	None	Dual-flared	18/23 20/25 23/28 25/31	6/8/10 6/8/10 6/8/10 6/8/10/13.5	Yes	Biodegradable

*Length means the whole length of the stent including the stent head, body, and tail.

of these rigid prostheses was associated with a high complication rate (close to 18%) and a mortality rate up to 9%.¹³ With the development of metallic stents, accumulated evidence supports the premise that metallic stents are better than rigid prostheses in terms of the complication and hospitalization rates and the overall cost efficacy.^{13,14}

Metallic stents can be classified into three types according to the status of the stent covering, i.e., uncovered, partially covered, and fully covered. This classification generally conforms to the development timeline of metallic stents. For managing refractory, benign esophageal strictures, stents have been used based on the concept that the implanted stent can dilate the stricture continuously for weeks and which may result in sustained lumen patency after its removal.¹⁵

However, the initial reports regarding the placement of self-expandable, bare stents were discouraging. Although the strictures improved immediately after bare-stent insertion, symptom recurrence occurred several weeks later due to tissue growth through the mesh of the stent. Cwikiel et al¹⁶ inserted uncovered stents in pigs and found that an inflammatory reaction with fibrotic activity and degeneration of the muscular layers in the esophageal wall occurred. They also placed uncovered stents in five patients with benign strictures and two of them developed new strictures. Song et al¹⁷ inserted uncovered stents in three patients, all of whom developed new strictures. They attempted to remove the stents under endoscopy but failed as the stent wires were embedded in the esophageal wall.

Since the invention of partially covered, self-expandable metallic stents (PC-SEMSs), which were originally designed for malignant esophageal strictures, they have also been used for the treatment of benign esophageal strictures as the membrane can prevent tissue ingrowth and prolong stent patency. However, the big difference of stenting in benign and malignant strictures is that the stent must be removed after a short period due to delayed complications. The tissue embedding and ingrowth at the

bare ends of the stent make the stent extraction difficult, and the procedure is associated with several complications, such as perforation, bleeding, and stent fracture.¹⁸ If stents are not removed for a long time, other complications can also occur, including recurrent obstruction caused by tissue ingrowth or stent migration and stent erosion into mediastinal structures.^{6,19} In one early case study, three patients with benign esophageal strictures who underwent partially covered Wallstent (Boston Scientific, Natick, MA, USA) insertion all developed further strictures and two patients had stent migration.²⁰ In another study, major complications occurred in four of eight patients and one patient developed fatal hemorrhage due to stent erosion into the aorta.²¹ Because of these serious adverse events, PC-SEMSs are also unsuitable for use in benign esophageal strictures.

To overcome the problem of recurrence of stricture or difficulty in stent removal caused by tissue ingrowth though the stent mesh of PC-SEMSs, fully covered, self-expandable, metallic stents (FC-SEMSs) have been used. In two, comparative studies, the authors found that tissue formation was more common in patients with PC-SEMSs than in those with FC-SEMSs.^{22,23} In another study, the authors retrospectively investigated 214 patients with benign esophageal strictures and who underwent 329 stent extractions. They found that the extraction of FC-SEMSs were safer and associated with fewer complications compared with that of PC-SEMSs.²⁴ Kim et al¹⁰ also published data regarding the use of FC-SEMSs to treat benign strictures in 55 patients and showed that the symptoms improved in all patients after stent insertion.

However, stent-associated complications have also occurred, e.g., one being stent migration (25%) and the other tissue overgrowth (31%).¹⁰ In some small series, the reported migration rates of FC-SEMSs were even higher, ranging from 33% to 48%.^{25–27} This may be explained by the fact that the FC-SEMSs are insufficiently anchored to the esophageal wall.²⁸ To prevent migration, the endoscopic techniques of anchoring the proximal flare of the stents to the esophageal wall with clips or sutures might be effective.

tive.^{29,30} Moreover, stents designed to prevent migration were also studied, although these outcomes are still unsatisfactory. In one study of a new antimigration stent used for malignant dysphagia, the migration rate was 20%.²²

Although tissue ingrowth can be almost eliminated, the recurrent stricture caused by tissue overgrowth at both ends of the stent is still a problem. The longer the stent is placed, the more likely the stricture recurs due to the formation of granulation tissue. On the other hand, if the stent is retracted too early, the dilation effect may be weak. Up to now, little consensus has been reached regarding the optimal duration of stent placement in patients with benign strictures and with the reported duration ranging from two weeks to two years.³¹ Song et al³² suggested removing a stent after 4 to 8 weeks on the basis of the low rates of stent-induced strictures during that time period. Fukuda et al³³ recommended the optimal time for removing a stent as 3 to 4 weeks, according to the endoscopic findings of hyperproliferative tissue two weeks after stent insertion. Perhaps the optimal duration time should be individualized depending on the etiology and morphology of each stricture.

Other properties of self-expandable metallic stents

The metallic materials of stents

Stainless steel (SS) and nitinol are the commonly used materials for esophageal stents. Although the SS and nitinol stents did not differ in terms of stent patency, SS stents were associated with a higher rate of severe pain after stent placement.³⁴ The possible explanation is that the SS stents have a stronger radial force and lack longitudinal flexibility.³⁴ Another advantage of nitinol stents is that they are magnetic resonance compatible. Magnetic resonance examinations can be performed after stent placement.^{6,35} Moreover, the diameter of the SS wire and the SS stent introducer are larger than those of nitinol stents. Therefore, nitinol stents are preferred and are becoming more frequently used.

The coating materials of covered stents

The ideal stent membrane should have both physical and chemical stability which can prevent tissue ingrowth. The typi-

cally used materials for stent membranes are silicone, polyurethane (PU), and polytetrafluoroethylene (PTFE). However, as the silicone-covered stents are insufficiently flexible, the membrane is often damaged while the stent is being placed into the introducing tube or while the introducing tube is being withdrawn.³⁶ PU membrane degradation was found to occur in patients in several studies and with a rate of 5% to 8%, which is susceptible to acid fluid in patients with gastroesophageal reflux.^{34,37,38} Some studies have shown that stents coated with PTFE membranes seemed to be more stable than those with PU, although with a 0.7% rate of PTFE membrane separation from the nitinol wire in patients with malignant esophageal strictures.^{34,36,39}

The shape of stents

Most of the shapes of metallic stents are dumbbell or flared. Na et al³⁴ found that flared stents had significantly higher migration rates than dumbbell-shaped stents during the treatment of malignant esophageal strictures (Fig. 1). van Heel et al⁴⁰ compared two types of metallic stents used for malignant esophageal strictures, one of which was Ultraflex (Boston Scientific) with a solo-flared end, and the other was Evolution (Cook Medical, Bloomington, IN, USA) with a dumbbell shape. The results showed that the Ultraflex stent was associated with more stent dysfunction. The authors ascribed this to the different stent designs and mentioned that the dumbbell shape may prevent migration. However, as the data regarding stents used for benign strictures are limited, this finding must be confirmed by further comparative studies.

Stent retrievability

As the early designed stents were not removable, they are not a good option for benign strictures because complications such as tissue growth, stent migration, and stent fracture can occur. The innovation of retrievable stents has reduced these complications associated with long-term dwelling. In addition, these stents can easily be repositioned or replaced with a new stent if they migrate and/or lose their function. Therefore, the technological development of retrievable, expandable stents was a turning point in managing benign and malignant esophageal strictures. These stents can be either fluoroscopically removed using a stent re-

Fig. 1. Photographs show a dumbbell-shaped stent (A) and a dual-flared stent (B).

moval set or endoscopically removed using forceps.

Stent design for proximal esophageal strictures

For proximal esophageal strictures, stents should be placed with caution as patients may feel uncomfortable after stenting due to the foreign-body sensation. Conio et al⁴¹ used custom-made Niti-S stents (Taewoong Medical, Gimpo, Korea) to treat seven patients with post-radiation strictures of the hypopharynx. The stent body diameters were smaller than usual. Their results showed that the dysphagia symptoms significantly improved in six of seven patients after stent placement.

Self-Expandable, Esophageal, Plastic Stents

Currently, the Polyflex (Boston Scientific) self-expandable plastic stent (SEPS) is the only U.S. Food and Drug Administration-approved stent for benign esophageal strictures (Fig. 2).⁴² It is made of a polyester mesh with an inner coating of silicone that extends along the entire length of the stent.¹⁹ Both ends of the stent are covered with silicone in order to reduce granulation tissue formation. The flared design of the proximal end of the stent is to prevent stent migration. Because it is made of plastic, there are three, radiopaque markers at the proximal, middle, and distal points of the stent to facilitate visualization during deployment. Before placement, the stent must be loaded into a delivery system with a large profile (12 to 14 mm in diameter). Under endoscopic guidance, the stent can be removed or repositioned with grasping forceps. The stent has the advantage of being economical as it can be removed, reloaded, and placed again. Its disadvantage is that the delivery system is larger and stiffer compared with most SEMSs, and which makes the delivery more difficult and usually requires dilation of the stricture prior to stent placement.¹³

In an early study, Evrard et al⁴³ reported that the symptoms in 17 of 21 patients with benign strictures had distinctly improved by the mean 21-month follow-up. Repici et al⁴⁴ found a similar result that 12 of 15 patients with benign strictures remained symptom-free at a mean follow-up of approximately two years. However, the results of subsequent studies showed a lower, long-term clinical success (less than 50%) and more complications.^{45–52} Holm et al⁴⁵ performed stent placement in 30 patients with different causes of strictures, e.g., anastomosis, postradiation, etc., and only 17% of these patients showed a durable response. Other reports have also shown that only 6% to 30% of the patients experienced long-term dysphagia improvement.^{45,47}

Fig. 2. Photograph shows a self-expandable plastic stent with capture basket for stent preloading into the delivery system (arrowheads). Reused from the book chapter of Laasch⁴² (Self-expandable stents in the gastrointestinal tract. New York: Springer; 2013, p. 51–87) with permission.

Regarding the complications, granulation-tissue formation was very rare after Polyflex stent placement, as it was observed in only one of nine studies.³¹ This could be explained by the plastic material of the Polyflex stents used, and which differs from that of metallic stents. However, stent migration is more common compared with FC-SEMSs. In the largest prospective study, migration occurred in 22% of 40 patients with benign strictures after stent placement for only four weeks.⁴⁷ In most of other reports, the migration rates were higher than 50%.³¹ The high migration rate may be caused by the fully covered stent design and its solo-flared structure without shoulders. The migration rate is also associated with the etiology and location of the stricture. Migration was seen more often in peptic strictures, followed by anastomotic strictures, and post-radiation strictures.^{47,53} Meanwhile, the migration rates were higher in distal and proximal strictures compared to mid-esophageal strictures.⁴⁷ Other serious complications have included perforation, fistula formation, bleeding, and the inability to remove the stents.⁵⁴ There was even one patient who died from stent-induced, massive bleeding.⁴⁷ These drawbacks of the current SEPS limit its use for benign strictures.

Biodegradable Stents

One disadvantage of metallic or plastic stents for benign strictures is that the stent should be removed after a certain period of time. The emerging use of biodegradable stents is likely to solve this problem as they are made of materials (polylactide/polydioxanone) which can be metabolized by the body and thus they do not require manual removal (Fig. 3).^{19,42} As biodegradable stents are currently uncovered, granulation tissue can grow through the mesh which can anchor the stent. However, the extent of tissue hyperplasia induced by biodegradable stents is lower than that of uncovered metallic stents. Repici et al⁵⁵ published a prospective study investigating a new biodegradable stent (ELLA-CS, Hradec Kralove, Czech) used for the treatment of benign strictures in 21 patients and found that only one patient had stent obstruction caused by tissue in- and over-growth. In their study, stent migration only occurred in two patients (9.5%) and the stents in the re-

Fig. 3. Photograph shows a biodegradable stent and spontaneous disintegration after being exposed to air for 18 months. Reused from the book chapter of Laasch⁴² (Self-expandable stents in the gastrointestinal tract. New York: Springer; 2013, p. 51–87) with permission.

maintaining patients were almost completely fragmented at the time of the three-month follow-up endoscopy. At a median follow-up of 53 weeks, 45% of these patients were dysphagia-free. Only minor complications, including severe pain (three patients) and minor bleeding (one patient), had occurred and there were no major complications. This stent is made of polydioxanone absorbable, surgical suture material. The integrity and radial force of the stent usually last for six to eight weeks after placement. The disintegration usually occurs by 11 to 12 weeks and can be accelerated by low pH. During the degeneration process, the stent material is partly absorbed and partly passes through the gastrointestinal tract. Before placement, the stent should be loaded into a 28-F delivery system. Because the stent body is transparent, radiopaque markers are added at both ends. Hirdes et al⁵⁶ also performed a prospective, follow-up study in 28 patients with refractory, benign, esophageal strictures. They implanted a total of 59 stents and found that single, biodegradable stent placement was only temporarily effective in the majority of patients and was associated with considerable complications, such as severe pain and vomiting. Only 25% of the patients were free of dysphagia for six months or more after the first stent placement. Sequential, biodegradable stent placement can be an effective option in order to avoid serial dilations. According to their clinical experience, if stent migration occurs, removal of the stent is unnecessary as the stent can be degraded faster when it enters the stomach due to the low pH of the gastric fluid.

Saito et al⁵⁷ developed an Ultraflex-type, biodegradable stent by knitting poly-L-lactic acid monofilaments. The radial force of this stent is comparable with that of commercially available metallic stents. In their study, 13 patients with benign strictures underwent poly-L-lactic acid stent placement. Stents spontaneously migrated and were excreted in 10 of the 13 patients at 10 to 20 days after placement. At a follow-up of seven months to two years, all patients remained symptom-free. The authors explained that the high stent migration rate may have been due to a loss of patency as the stents degrade. The other reason may have been that the stent placement was for the prevention of stenoses after endoscopic submucosal dissections in seven patients of this group.

Canena et al¹¹ compared the three types of temporary stents used for the treatment of refractory, benign esophageal strictures. The three types of stents were a biodegradable stent, FC-SEMS, and SEPS. Their results showed that the biodegradable stent, FC-SEMS or SEPS were associated with long-term relief of dysphagia in 30%, 40%, and 10% of their patients, respectively. There were more stent migrations in the SEPS groups than in the other two groups, and which, therefore, required more interventions.

Drug-Eluting Stents

The mechanism of tissue in- and overgrowth following stent placement in the esophagus is that the pressure imposed by the stent on the esophageal wall decreases the blood supply to the tissue and leads to ischemic damage. As time passes, complications, such as granulation tissue caused by ischemic necrosis, ulcers, and fibrosis, cause esophageal restenosis.⁵⁸ Therefore, using drugs to prevent or alleviate tissue fibrosis after stent placement is an appealing concept. The emergence of drug-eluting stents (DESs) provides such an option. DESs have previously been developed for the prevention of vascular restenosis and have recently been considered for the management of gastrointestinal diseases.

There are several kinds of drugs, such as paclitaxel and IN-1233, being studied for treating benign esophageal strictures. Paclitaxel is a type of antineoplastic agent. In addition to its

antineoplastic effect, this drug also has anti-proliferative and anti-angiogenic effects.^{15,58} These effects could possibly allow paclitaxel to be used for the treatment of stent-induced tissue proliferation in benign esophageal strictures. The anti-proliferation effect of paclitaxel has been proven to be dose-dependent. A high dose could be more effective, but also poses the problem of potential side effects, such as neutropenia and neurotoxicity, as shown in systemic chemotherapy. However, unlike the high-dose systemic chemotherapy which requires a high concentration in plasma, the total dose and the plasma level of paclitaxel for local drug delivery are low. Some studies have shown that the plasma levels of paclitaxel in patients who underwent systemic chemotherapy were up to 1,000-fold higher than the plasma levels that would result from local delivery.⁵⁹⁻⁶¹ In an animal study of DES for benign esophageal strictures, paclitaxel was dissolved in a non-degrading silicon polymer and its emission was toward the esophageal mucosa.⁵⁸ The result showed that DES could inhibit granulation tissue growth and fibrosis formation and that the stents could be easily removed without complication at eight weeks after their placement.⁵⁸

Recently, Kim et al⁶² evaluated the efficacy of the IN-1233-eluting covered stent for preventing tissue hyperplasia in a rabbit esophageal model. It is known that transforming growth factor β and its receptor, activin receptor-like kinase (ALK)-5, have important roles in fibrosis proliferation.⁶² 3-((4-(6-methylpyridin-2-yl)-5-(quinolin-6-yl)-1H-imidazol-2-yl) methyl) benzamide (IN-1233) is a type of ALK-5 inhibitor which has been proven to be effective for preventing urethral tissue hyperplasia in a rat model.⁶³ On the basis of the results in the urethral model, the authors used the IN-1233-eluting covered stents in the rabbits' esophagus and found that the DES could reduce granulation tissue formation. Based on these pioneering studies, DES seems to be a potential solution for decreasing or preventing tissue hyperplasia induced by stent placement. Before its human application, additional studies are warranted to further evaluate its efficacy and safety.

Conclusion

Stent placement has been regarded as an essential complementary procedure to balloon dilation for benign esophageal strictures. Clinical practice and knowing the advantages and disadvantages of different stents encourage esophageal stent evolution. From uncovered to covered, from unretrievable to retrievable, from SS to nitinol or polyester, these changes now make the retrievable FC-SEMS and SEPS stents useful options for refractory benign esophageal strictures, although SEPS is not strongly recommended as it is associated with more technical difficulties and late migration compared with FC-SEMS. However, granulation tissue overgrowth and stent migration remain the two major problems. The emergence of the biodegradable stent and the drug-eluting stent bring the hope of solving these problems. Further studies are warranted to establish their definite role.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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